Configurable Power Inverter for Magnetic Hyperthermia for Cancer Treatment Purpose

O. García[1], A. Bravo[1], N. Moreno-Arrones[1], A. Gutiérrez[1], P. Alou[1], J.A. Oliver[1], J.A. Cobos[1], J. Uceda[1], E. Aznar[2], R. Martinez-Máñez[2], C. Sánchez[3], O.Casanova[4], J. Serrano[4], F. del Pozo[4]

1 Centro de Electronica Industrial (CEI), Universidad Politecnica de Madrid (UPM), Madrid, Spain
2 Institute of Molecular Recognition and Technological Development (IDM), Universidad Politécnica de Valencia (UPV), Valencia, Spain. Networking Center Biomedical Research in Bioengineering, Biomaterials and Nanomedicine, Instituto de Salud Carlos III, Spain.

3 Escuela Politécnica Superior, Universidad San Pablo-CEU, Campus Montepríncipe, Boadilla del Monte, Madrid, Biomedical Research Networking Center in Bioengineering Biomaterials and Nanomedicine
4 Centre for Biomedical Technology (CTB), Technical University of Madrid (UPM), Madrid, Spain. Biomedical Research Networking Center in Bioengineering Biomaterials and Nanomedicine

Abstract— This paper shows an example of collaboration of people of different areas working together and achieving a promising result. In this case, a power electronics circuit allows the generation of high frequency magnetic field that can be used to increase the temperature of cancer cells previously invaded with magnetic nanoparticles. Although the research is one of the early stages, the results show that this technique could be a real option in the future. The circuit designed for this purpose is a high frequency phase-shift inverter implemented with SiC devices and natural ZVS. A big part of the design effort has been focused in the optimization of the power inductor that contains the sample with the nanoparticles.

I.- Introduction

Thermal therapies have been used along decades as a mean to help the recovery from several diseases, mainly as a complementary mean to the use of drugs and or mechanical manipulations depending on the specific application [1]. In particular, cancer is a quite well suited disease to be treated with heat because cancer cells are more sensitive to heat than healthy ones. In fact, temperature increases over 43º for several minutes can seriously damage those cells, which die by apoptotic mechanisms some hours after the treatment, while the rest of the cells survive [2]. Heating is also a well-suited therapy against cancer because tumors are quite un-receptive to therapeutic molecules for several reasons, and especially in hard to access places like the brain parenchyma [3]. However, either using ultrasounds or different kinds of electromagnetic sources, all conventional techniques suffer from the same drawbacks: not enough spatial resolution and precision in the localization of the volume where to deposit the thermal energy, and, the worst, the need for the applied radiation to cross healthy tissues to get to the desired area, tissues that, then, can receive an even larger amount of energy than the targeted ones becoming unnecessary heated as well [4]. Although some efforts are in progress to improve conventional techniques like the case of Focused Ultrasounds, other new ones are being investigated to overcome those limiting performances. They use some intermediate agents previously deployed in place. These agents receive the energy, assuming it travels throughout the living tissues without affecting them. They convert part of the energy into heat, so heating their surroundings. This way, each problem is fitted at a different level: spatial resolution and localization is solved by correctly deploying the agents, what is mainly a chemo-physiological problem, and the amount of energy and its application is mainly a matter of the energy source.

One of these new techniques is the so-called Magnetic Hyperthermia [5,6]. The energy comes from a radiofrequency source of some hundreds of kilohertz and as intermediate agents nanoparticles of ferromagnetic materials are used, sizing some tenths of nanometers. Radiofrequency also heats the living tissues due to their conductive character, but this drawback can be corrected by limiting the power of the source. This inconvenience is largely compensated by the fact that the corresponding wavelength is large enough to bring the energy no matter the place in the body. The particles become magnetized when the radiofrequency is present and start vibrating, either their whole body or their inner magnetic momentum, or both. Whatever the mechanism of interaction between particles and radiofrequency, dissipative the amplitude of the magnetic field to maximize the magnetization of the particles. The net power transmitted mechanisms transform the mechanical energy into heat. At this point one field of research is how to place the particles in place (and what kind of particles) in a safe and effective way, and other is how excite those particles to maximize the heating. Of course, the goal is to reduce as much as possible the amount of delivered particles and energy, while keeping the therapeutic efficacy. Although both fields are tightly related and the whole approach could be seen as composed of many more faces, there is room to work with some independence in the excitation problem field. At this point, the state of the art is based on the use of sinusoidal waveforms for the radiofrequency emitter, since they are easily obtained at the moderately high power needed from the resonant circuits. Actually, it is not so much a matter of power, as of to heat the particles is rather small since the amount of particles is not so high. However, the ferromagnetic material when distributed as particles well under a micron diameter, to mention a common limit, becomes super-paramagnetic. Super-paramagnetic materials do not develop remanent magnetic fields and need higher magnetic saturation. The more the magnetization of the particles, the larger the amount of radiated energy converted into heat. Therefore, the issue of the amplitude is of great importance. Since the resonant circuits can provide radiofrequency power of high amplitude while not providing much power that is not needed anyway, they have been generally the instrument of choose.

Few works have been carried on to explore other waveforms, although demonstrating for ferromagnetic particles, a higher efficiency than conventional sinusoidal excitation [7]. The mechanism converting the radiofrequency energy in heat is different in the case of ferromagnetic materials. However, since the size of the particles made of super-paramagnetic materials is smaller, they are very useful as intermediate agents in the living tissues for histological reasons.

The question about the use of other waveforms with super-paramagnetic particles is open. The interaction of these particles with the liquid environment where they are in suspension in the normal case of being used in biological fluids, is really complex and still rather unknown. However, a previous work, still unpublished, points out to the existence of a dependency of the losses in the particles (they behave as the secondary in a very particular transformer) on the amplitude of the magnetic field different from the theoretical one for low fields. At the same time, the stationary movement of the particles achieved when using harmonic excitation could tend to reduce the efficacy of the dissipation mechanisms. To check all these issues in the search for more efficient ways to provide the radiofrequency energy for future magnetic hyperthermia based therapies, we have developed a new instrument as it is presented in what follows.

II.- Power Inverter

The circuit required to generate the alternating magnetic field is a full bridge inverter (see figure 1). Nothing special is required since a simple phase shift control is enough to configure the maximum current, the current slope and the switching frequency. From the point of view of the power electronics design, the main challenge is to reduce the power losses when it operates in the MHz range.

The main specifications that have been fixed for this configurable inverter are:

- Input voltage: up to 500V
- Switching frequency: up to 2MHz
- Peak current: up to 15A

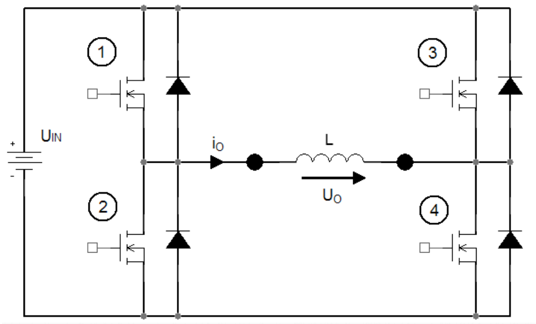

Figure 1.- Power inverter

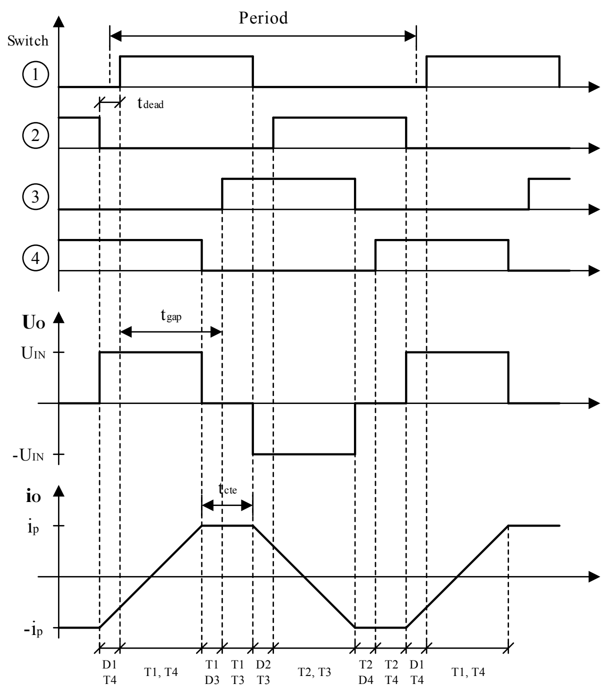

Figure 2.- Gate signals, output voltage and output current

Playing with both the input voltage and the phase-shift angle, it is possible to vary the trapezoidal output current (see figure 2) to triangular or square waveform. The converter will work in different operating points to perform experiments with the samples of nanoparticles.

It is important to realize that since the load is an inductor, it is very easy to achieve zero voltage switching (ZVS) with an appropriate timing of the gate signals [8-11]. Optimization of the power stage in terms of power losses has been carried out, obtaining a circuit that provides the desired current with relatively small losses. The power MOSFETs are SiC Cree devices.

III.- Optimization of the Inductor

One of the main challenges of this project is to optimize the power inductor. It should be considered that the objective is to achieve a particular magnetic field in the center of the inductor trying to reduce the power losses on it. It also should be considered that there are some important physical constrains that limit the degrees of freedom in the design. In particular, the probe with the nanoparticles (explained in the experimental results sections) forces to have a minimum radius of 3 cm.

The preliminary inductor used in the experiments is shown in figure 3. This inductor is made with 10 turns of 4mm diameter copper wire. It is 10 cm tall and it is possible to see that there is a big separation between turns (around 1 cm but not homogeneous). With this inductor and with a peak current of 8A, the flux density in the center is around 0.6mT (this value has been obtained from the finite element analysis simulation). It is obvious that this inductor has a very high leakage flux due to the separation of the turns and a further optimization is mandatory.

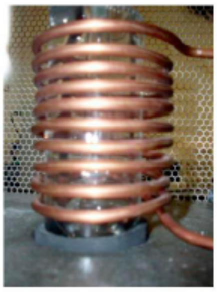

Figure 3.- Picture of the preliminary inductor

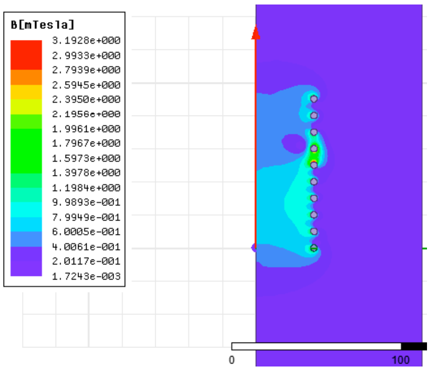

Figure 4.- FEA simulation of the preliminary inductor

The purpose in this section is to design an inductor with air core that it is able to provide a high electric field in the center of it, minimizing the current. The factors that have been considered for this optimization are: number of turns, wire diameter and separation of the turns; the radius of the inductor has not been changed, since we would like to use the same setup. The optimization of the inductor has been carried out using a finite element analysis tool, namely Maxwell 2D. Table I shows the main data obtained form these simulations and figure 5a shows the simulation of the proposed inductor and 5b a picture of it. With this new inductor, the flux density in the sample is three-times higher (1.95mT).

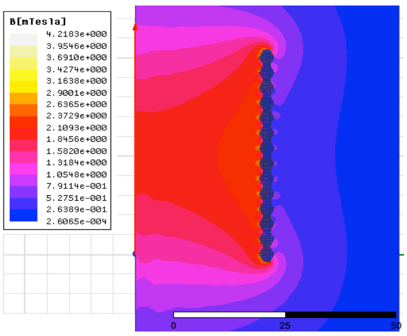

Figure 5a.- Simulation of the optimized inductor

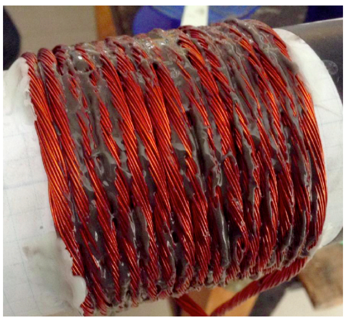

Figure 5b.- Optimized inductor

IV.- Experimental Results

In this stage of the research, the main objective is to design a circuit that generates a configurable magnetic field and to measure its effect on the temperature of the sample with a particular concentration of nanoparticles. Therefore, it is very important to assure a very good thermal isolation between the probe and the inductor and the room temperature. For this purpose, the nanoparticle will be in the center of a structure with a vacuum chamber surrounded by a constant temperature water flux. With it, the effects of the power losses on the copper wires of the inductor do not have an impact on the temperature of the nanoparticles.

The inverter has been designed suing SiC MOSFETs that show a better performance for this design compared with Si. Using these devices, only a small heatsink is required (see inverter in figure 6). For the control stage, a specific board has been designed (see figure 7). This board has an internal FPGA and an interface that makes very easy to change phase angle, dead times and switching frequency that were part of the original requirements for the equipment.

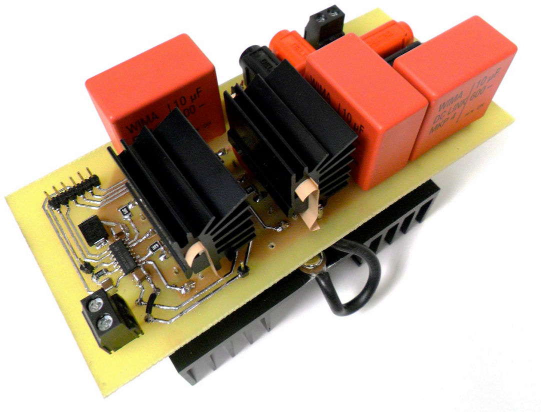

Figure 6.- Power inverter designed for these experiments

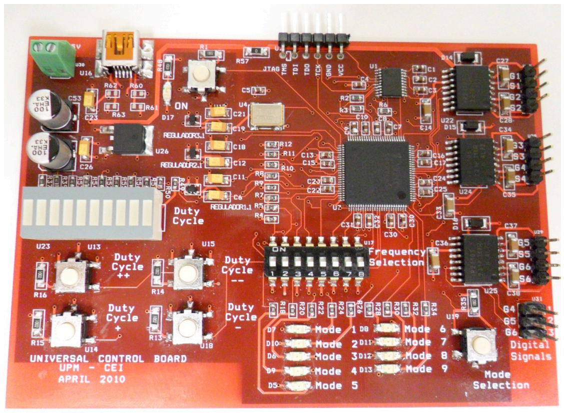

Figure 7.- Control board of the inverter

Several experiments have been carried out to measure the effect of the magnetic field in the sample (see Table I). The sample was made with 14nm Fe3O4 nanoparticles. Figure 8 shows the shape of the current through the inductor (i.e. magnetic field) in test #4.

Test	Frequency (kHz)	Shape of field	Voltage (V)	Current (A)	Time (min)	ΔTemperature (ºC)
#1	303	Trapezoidal	195	12	24	1.5
#2	303	Trapezoidal	235	14	10	1.5
#3	510	Trapezoidal	286	10.5	34	1.6
#4	800	Trapezoidal	380	9	35	2.1
#5	800	Trapezoidal	470	11	25	2.1
#6	800	Square	490	6	28	1.3
#7	800	Triangular	205	6	20	2.7
#8	800	Triangular	410	12	13	2.7
#9	1315	Square	500	6	25	1.7
#10	1315	Triangular	370	6	20	2.2
#11	1315	Triangular	500	8.2	10	2.2

Table I.- Experiments carried out using the inverter and the inductor. The temperature is measured in a thermally-isolated probe with nanoparticles located in the center of the inductor

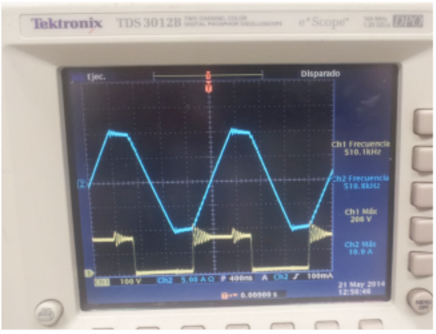

Figure 8.- Capture of the current through the inductor (5A/div and 400ns/div)

The first conclusion that can be extracted is that with this equipment, significant increments of temperature are achieved compared with previous experiences. In most of the cases, these tests are useful to see dependences but not to extract quantitative values. The temperature increments seem to be very correlated with the amplitude of the current; the same can be said about the frequency of the magnetic field, but not in all cases. At this moment, it is not possible to extract clear conclusions about the influence of the shape of the field in the temperature. Anyhow the results seem very promising and now that the equipment is available, many more experiments will be carried out.

Figure 9 shows two experimental data obtained from the tests. The obtained temperature increments can be enough to kill the bad cells by inducing localized fever in the patient.

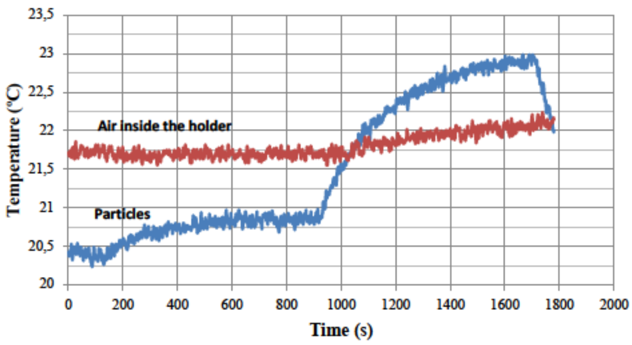

Fig. 9a.- Experimental temperature increment in test #5

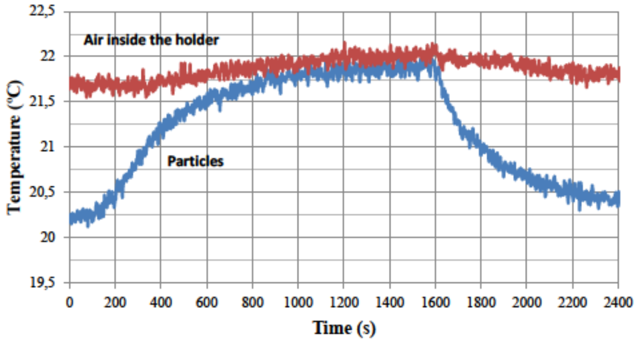

Fig. 9b.- Experimental temperature increment in test #10

V .- CONCLUSIONS

The purpose of this work is to design a configurable power inverter to induce heating in a sample with a big concentration of nanoparticles, as a first step for the magnetic hyperthermia technique. The inverter allows tests with different parameters of the magnetic field such as frequency, intensity and shape. The combination of these three parameters may show the best way to continue the research with this technique. By the moment, temperature increments beyond 2.5ºC have been achieved, being a very good result compared with the previous experiences. From the point of view of power electronics, the success is due to an optimized design of the power stage, and especially to the inductor, that maximized the field in the position where the sample with nanoparticles is located.

IV.- REFERENCES

[1] W. C. Dewey, L. E. Hopwood, S. A. Sapareto, and L. E. Gerweck, "Cellular responses to combinations of hyperthermia and radiation," Radiology, vol. 123, no. 2, pp. 463–474, 1977.

[2] Wang, X.; Yang, L.; Chen, Z.; Shin, D.M. Application of Nanotechnology in Cancer Therapy and Imaging. A Cancer J Clin 2008, 58, 97–110

[3] Brandes A A, Tosoni A, Franceschi E, Reni M, Gatta G and Vecht C 2008 Glioblastoma in adults Crit Rev Oncol Hematol 67 139-52

[4] A.B. Salunkhe, V.M. Khot and S.H. Pawar, Magnetic Hyperthermia with Magnetic Nanoparticles: A Status Review, Current Topics in Medicinal Chemistry, 2014, 14, 000

[5] G Vallejo-Fernandez, O Whear, A G Roca, S Hussain, J Timmis, V Patel2 and K O'Grady1,2Mechanisms of hyperthermia in magnetic nanoparticles, J. Phys. D: Appl. Phys. 46 (2013) 312.001 (6pp)

[6] Hiroaki Mamiya, Recent Advances in Understanding Magnetic Nanoparticles in AC Magnetic Fields and Optimal Design for Targeted Hyperthermia, Journal of Nanomaterials, Volume 2013, Article ID 752973, 17 pages

[7] Eiji Kita, Tatsuya Oda, Takeru Kayano, Suguru Sato, Makoto Minagawa, Hideto Yanagihara, Mikio Kishimoto, Chiharu Mitsumata, Shinji Hashimoto, Keiichi Yamada and Nobuhiro Ohkohchi, Ferromagnetic nanoparticles for magnetic hyperthermia and thermoablation therapy, J. Phys. D: Appl. Phys. 43 (2010) 474011 .

[8] J.A. Sabate,V. Vlatkovic, R.B. Ridley, F.C. Lee, B.H. Cho, "Design considerations for high-voltage high-power full-bridge zero-voltage-switched PWM converter," Applied Power Electronics Conference and Exposition, 1990. APEC '90, Conference Proceedings 1990., Fifth Annual , vol., no., pp.275-284, 11-16 March 1990.

[9] G. Hua, F.C. Lee, "Soft-switching techniques in PWM converters", Industrial Electronics, IEEE Transactions on , vol.42, no.6, pp.595-603, Dec 1995.

[10] Ki-Bum Park; Chong-Eun Kim; Gun-Woo Moon; Myung-Joong Youn; , "Voltage Oscillation Reduction Technique for Phase-Shift Full-Bridge Converter," Industrial Electronics, IEEE Transactions on , vol.54, no.5, pp.2779-2790, Oct. 2007.

[11] R. Redl, N.O. Sokal, L. Balogh, "A novel soft-switching full-bridge DC/DC converter: Analysis, design considerations, and experimental results at 1.5 kW, 100 kHz," Power Electronics Specialists Conference, 1990. PESC '90 Record., 21st Annual IEEE , vol., no., pp.162-172, 0-0 1990.